



DEPARTMENT OF HEALTH & HUMAN SERVICES

New York District

Food & Drug Administration
850 Third Avenue
Brooklyn, NY 11232

WARNING LETTER AND REQUEST FOR RECALL

HAND DELIVERED

March 8, 1999

Chris Plumeri, President
Brett Holzer, Vice President
Invigorate International
83 West 104th Street
New York, NY 10025

Ref: NYK 1999-036

Dear Sirs:

This letter concerns your product Invigorate. The product label declares as an ingredient 2(3H)-Furanone di-hydro, also known as gamma-butyrolactone (GBL).

Representatives of the Food and Drug Administration (FDA) New York District Office spoke with you on March 4, 1999 to express FDA's concerns about the safety and legality of your product and to determine your intentions with respect to the continued marketing of the product. On that date, you informed our representatives that you are not willing to recall the product, Invigorate, already in the marketplace.

As discussed below, FDA has serious public health concerns about products such as yours that contain GBL as an ingredient. Because of these concerns, FDA has made available a talk paper to alert the public. FDA is prepared to pursue appropriate legal sanctions under the Federal Food, Drug, and Cosmetic Act (Act), including seizure, injunction, and criminal prosecution, as necessary to protect the public health.

GBL is a potent pharmacological agent that is closely related to, and rapidly metabolizes into, the drug substance gamma-hydroxybutyrate (GHB). GHB is a drug substance that is legally available in the United States only as an investigational new drug for specified uses. There is considerable information available concerning the known physiological effects and toxicity of GHB. Its primary pharmacological effect is that of a central nervous system depressant. Toxicity is characterized by coma, depressed respiratory rate, low body temperature, slow heart rate, and vomiting.

FDA has received at least 55 reports of adverse effects associated with the use of a number of different products that contain GBL. Many of these reports indicate significant effects on mental status. In 19 cases, the consumers were reported unconscious or comatose, and a number of

these persons required intubation for assisted breathing. Other reported adverse events include seizures, vomiting, muscle spasms, respiratory depression (decreased breathing rate), and bradycardia (slow heart rate). One death of a GBL consumer was reported as being related to "idiopathic cardiac arrhythmia" and drug-induced sleep. The mean age of individuals reporting an adverse event was 29 years (range, 11 - 71 years), with at least five reported adverse events occurring in individuals under 18 years of age. The adverse events thus far reported for GBL-containing products are consistent with the known toxicity of GHB as reported in scientific literature.

GBL, like GHB, is a powerful hypnotic substance known to produce significant and potentially dangerous sedating effects. Therefore, FDA considers GBL-containing products, such as Invigorate, to be drugs as described in section 201(g)(1) of the Act. Such products are also new drugs, as defined in section 201(p) of the Act, which require FDA approval under section 505(a) of the Act prior to marketing. The marketing of new drugs without an approved new drug application is prohibited under section 301(d) of the Act.

Invigorate is also misbranded under section 502 of the Act. Among other reasons, the label and labeling of Invigorate do not bear adequate directions for use under section 502(f). The introduction or delivery for introduction into interstate commerce of misbranded drugs is prohibited under section 301(a) of the Act. The misbranding of a drug while held for sale after shipment in interstate commerce is prohibited under section 301(k) of the Act.

The agency recognizes that Invigorate is represented as a dietary supplement. The product does not meet the definition of a dietary supplement under section 201(ff) of the Act, however, because it is not marketed and used to augment or otherwise supplement the diet. GBL-containing products like Invigorate are being marketed and used to achieve the powerful pharmacologic, hypnotic, and sedative effects associated with GHB. Such products are not dietary supplements as described in section 201(ff)(1) of the Act.

Even if Invigorate could meet the definition of a dietary supplement, it is also a drug, and can be regulated as such. Moreover, even as a dietary supplement, it would violate other provisions of the Act. For example, the data collected thus far by the agency show that Invigorate presents a significant and unreasonable risk to consumers under section 402(f)(1)(A) of the Act.

We request that you take prompt action to correct these and any other violations associated with Invigorate and any other GBL-containing products marketed by your firm.

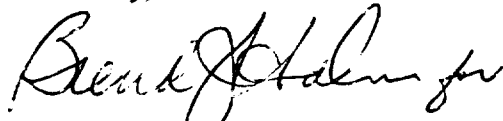
FDA is also requesting that you immediately cease manufacturing and distributing Invigorate and that you initiate a recall to the consumer level. We recommend that you follow FDA's "Enforcement Policy-Recalls (Including Product Corrections) -- Guidelines on Policy, Procedures and Industry Responsibilities" issued June 16, 1978, in conducting your recall, copy enclosed. Representatives of our New York District Office will be available to provide assistance in the

development of a recall communication as well as the strategy for retrieving and disposing of the recalled product. Our judgment concerning the effectiveness of your recall will largely be based upon your implementation of the recall guidelines.

Failure to immediately cease distribution of the product and conduct an immediate and effective recall could result in enforcement action by FDA without further notice. The Act provides for seizure of violative products, injunction against the manufacturers and distributors of violative products, as well as criminal sanctions against persons responsible for causing violations of the Act.

We request that you advise us in writing, within **twenty-four hours** of receipt of this letter, as to the specific steps that have been or will be taken to correct these violations, including an explanation of each step taken to assure that similar violations do not recur and the steps taken to recall the product. Your reply should be directed to Brenda J. Holman, Director, New York District, Food and Drug Administration, 850 Third Avenue, Brooklyn, NY 11232. You may submit your initial response via facsimile to (718) 340-7011.

Sincerely,

A handwritten signature in dark ink, appearing to read "Gary J. Dykstra", written over a horizontal line.

Gary J. Dykstra
Acting Associate Commissioner
for Regulatory Affairs

Enclosure: Recall procedures